UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,835	02/27/2004	Todd A. Thompson	054030-0052	8254

31096 7590 02/05/2007

GODFREY & KAHN, S.C.
780 N. WATER STREET
MILWAUKEE, WI 53202

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,835	THOMPSON ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-10 in the reply filed on 12/5/2006 is acknowledged. The traversal is on the ground(s) that a search of all claims would not present an undue search burden on the Examiner. Applicants further argue that Examiner has not presented a *prima facie* case for restriction of the instant claims. This is not found persuasive because the inventions of Groups I-IV are patentably distinct for the reasons set forth in the Restriction Requirement mailed 11/6/2006. While the compounds utilized in the claims of Groups I-IV are similarly classified, this is simply due to the fact that the classification system does not allow for the classification of an invention based on the condition to be treated. However, it is clear that a search for methods of treating acne would be distinct from a search for methods of treating prostate cancer. The diseases encompassed by "androgen-mediated disorder" are so diverse that to search them all would be an undue search burden (even though the same genus of compounds is being searched). This is further compounded by the fact that the instantly claimed compounds are well known in the art. A preliminary search reveals that the single specie recited in claim 2 is found in over 443 references published prior to 2004. To sift through all of these references for any mention of an "androgen-related" disorder would clearly be an undue burden on the Examiner.

Claims 11-24 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/5/2006.

The requirement is still deemed proper and is therefore made **FINAL**.

Status of the Claims

Claims 1-24 are currently pending and are the subject of this Office Action. Claims 11-24 are withdrawn from consideration. Claims 1-10 are presently under examination. This is the first Office Action on the merits of the claims.

Priority

This application claims the benefit of U.S. Provisional application 60/450,510, filed February 27, 2003. Support for the instant claims was found in the '510 application. As such, the earliest effective U.S. filing date afforded the instant claims has been determined to be 2/27/2003.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for inhibiting the growth of androgen-dependent tumor cells and delaying the progression of prostate cancer by administering the compounds recited in the instant claims, does not reasonably provide enablement for "preventing the occurrence or recurrence of prostate cancer". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

In the instant case, Examiner has interpreted claim 8 to read on the absolute prevention of prostate cancer. Support for this interpretation is found in the language of claim 8, which if read in its broadest reasonable interpretation, recites the prevention of prostate cancer (*i.e.* preventing the occurrence of prostate cancer).

While the *treatment* of prostate cancer is somewhat predictable (*e.g. in vitro* screening, *in vivo* models, clinical trials, etc.), the prevention of prostate cancer is not. It would take undue experimentation for the skilled artisan to practice the claimed method of preventing the occurrence of prostate cancer. There is simply no model system that could be used to test any particular compound for its efficacy in preventing prostate cancer. Further, the absolute prevention of prostate cancer, in its broadest reasonable interpretation, means that a subject will never, throughout his entire lifespan, get prostate cancer.

To enable claims to such a prevention of prostate cancer would require more than a demonstration that a particular compound is effective for *treating* prostate cancer. Applicants have provided no specific guidance or direction on how one skilled in the art could absolutely prevent prostate cancer by administering the claimed compounds.

As such, while the disclosure is enabling for inhibiting the growth of androgen-dependent tumor cells and delaying the progression of prostate cancer (both of which require the presence of prostate cancer cells), the disclosure is not enabling of a method of absolutely preventing prostate cancer.

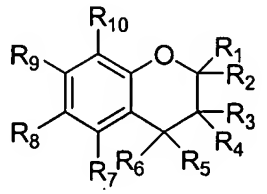
Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 7-8, 10-14 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 8 and 11 recite methods comprising administering a compound having the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently a *substituted* or unsubstituted C_1-C_3 alkyl group or H. The claims are indefinite because it is not clear what chemical substituents can be present on the C_1-C_3 alkyl groups (*i.e.* when R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and/or R_{10} are "substituted", with what are they substituted?). Thus, the metes and bounds of the claimed compounds are not clear and concise as required by 35 U.S.C. § 112, 2nd Paragraph. Claims dependent from claims 1, 5, 8 and 11 are included in this rejection. However, claims 2, 6, 9 and 15 recite a specific compound and are therefore not included in this rejection.

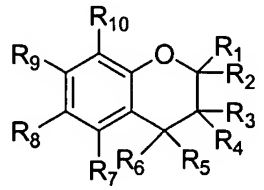
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

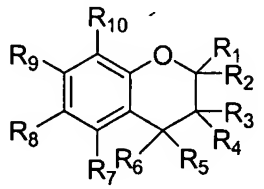
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Instant claim 1 is drawn to a method for inhibiting the growth of androgen-dependent tumor cells comprising administering a compound having the formula:



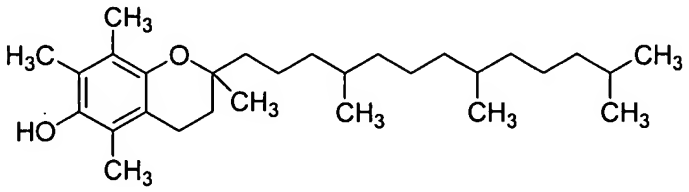
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently a substituted or unsubstituted C_1-C_3 alkyl group or H and R_8 is OH. Instant claims 5 and 7 are drawn to a method of delaying the progression of prostate cancer in a patient comprising administering a compound having the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently a substituted or unsubstituted C_1-C_3 alkyl group or H and R_8 is OH. The claims do not recite any limitations with respect to the substituent that may be present on the C_1 to C_3 alkyl group; however, it is noted that the instant disclosure states that the alkyl group can be substituted with a "carboxyl" group (page 14, line 5).

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Gunawardena *et al.* (The Prostate, 2000, vol. 44, pages 287-295) (cited by applicants).

Gunawardena *et al.* teach that vitamin E (α-tocopherol) and other antioxidants inhibit the growth of human prostate cancer cells through apoptosis (Abstract).



α-Tocopherol (Vitamin E)

The authors teach that antioxidants have been associated with a reduced risk of cancer in various tissues, including the prostate (page 288, left column). Three prostate cancer cell lines, DU-145 (androgen-unresponsive), LNCaP (androgen-responsive) and ALVA-101 (androgen moderately responsive) were used to test the effects of several antioxidants, including α-tocopherol on cell growth in culture (*id.* at right column). α-Tocopherol produced significant growth suppression of ALVA-101 and LNCaP cells compared to control (page 289, left column). The authors further disclose that androgens increase oxidative stress in androgen-responsive but not androgen-unresponsive cells such as PC-3 (page 292, left column). Vitamin E did not cause growth inhibition of in the androgen-unresponsive (DU-145) human prostate cancer cell lines, whereas it did significantly affect the growth of the androgen-responsive cell lines (*id.*). In summary, the authors conclude that the results suggest that antioxidants may retard human prostate cancer cell growth through mechanisms that activate apoptosis (page 292, right column).

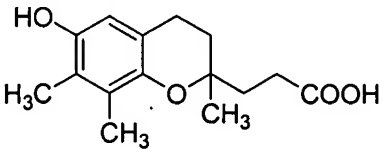
The reference thus teaches that α-tocopherol inhibits the growth of androgen-dependent prostate cancer cells. The limitations of instant claim 1 read on α-tocopherol (*i.e.* wherein R_1 is a "substituted" C_3 alkyl group).

Claims 1, 4-5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Azzi (U.S. Patent No. 6,350,776; Issued Feb. 26, 2002).

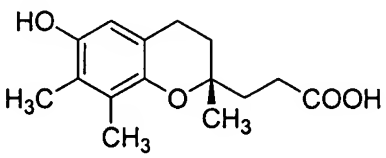
Azzi teaches a method of treating, inhibiting or preventing proliferative disorders, particularly cancer, by administering a combination of lycopene and α-tocopherol (Abstract). The agents are orally administered to a subject (col. 3, lines 3-8). The treatment of prostate cancer is taught in claim 2. The prevention of prostate cancer is taught in claim 9.

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wechter (U.S. Patent No. 6,242,479; Issued June 5, 2001).

Wechter teaches the administration of γ-tocopherol and γ-tocopherol derivatives as antioxidants which can be used to treat cancer (Abstract). For example, the γ-tocopherol derivatives useful in the invention include LLU-α and (*S*)-LLU-α (col. 3, lines 35-50).



LLU-α

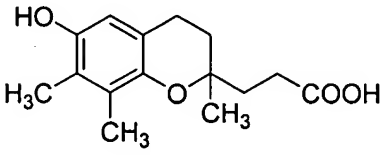


(S)-LLU-α

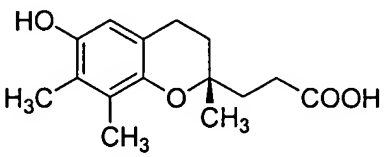
The treatment of prostate cancer is taught at col. 5, lines 19-25 and claims 11 and 32. The reference thus teaches the use of a sub-genus of the instantly claimed compounds in methods of treating cancer, including the instantly claimed prostate cancer. It is noted that the treatment of "prostate cancer" would naturally include the treatment of both androgen-dependent and androgen-independent prostate cancer.

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wechter (U.S. 2001/0031782 A1; Published Oct. 18, 2001).

Wechter teaches the administration of γ-tocopherol and γ-tocopherol derivatives as antioxidants which can be used to treat cancer (Abstract). For example, the γ-tocopherol derivatives useful in the invention include LLU-α and (*S*)-LLU-α (page 2, ¶¶ [0013] and [0014]).



LLU-α



(S)-LLU-α

The treatment of prostate cancer is taught at page 3, ¶ [0025] and claims 7-15. The reference thus teaches the use of a sub-genus of the instantly claimed compounds in methods of treating cancer, including the instantly claimed prostate cancer. It is noted that the treatment of "prostate cancer" would naturally include the treatment of both androgen-dependent and androgen-independent prostate cancer.

With respect to the above 35 U.S.C. § 102 rejections of claims 1, 3-5 and 7 and claims 1, 4-5 and 8 as being anticipated by Wechter (U.S. Patent 6,242,479) and Azzi (U.S. Patent No. 6,350,776), respectively, the "comprising" language of the instant claims allows for the presence of other active agents, including γ-tocopherol as taught in the '479 patent and lycopene as taught in the '776 patent (see M.P.E.P. § 2111.03). The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited

elements or method steps. See, *e.g.*, *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended").

Further, the limitations of instant claims 3 and 7 are inherent characteristics of the instantly claimed compounds. As such, any compound that is encompassed by the claimed genus will inherently have water solubility greater than that of vitamin E. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

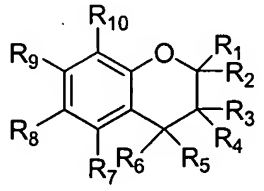
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Instant claims 1-4 are drawn to a method for inhibiting the growth of androgen-dependent tumor cells and claims 5-7 are drawn to a method of delaying the progression of prostate cancer in a patient comprising administering a compound having the formula:

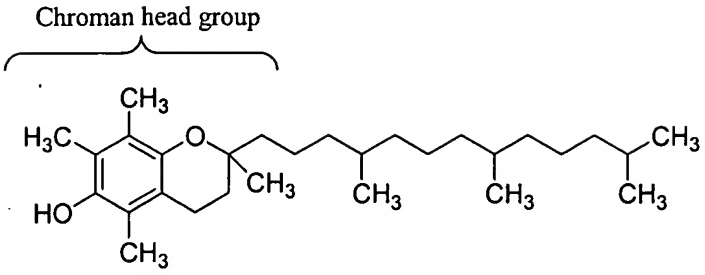


wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently a substituted or unsubstituted C_1-C_3 alkyl group or H and R_8 is OH.

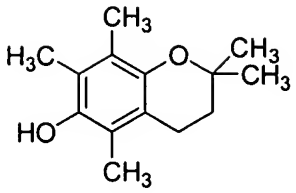
Claims 1-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunawardena *et al.* (The Prostate, 2000, vol. 44, pages 287-295) (cited by applicants) in view of Sheu *et al.* (Life Sciences, 1999, vol. 65, pages 197-206) (cited by applicants).

Gunawardena *et al.* disclose that vitamin E (α-tocopherol) and other antioxidants inhibit the growth of human prostate cancer cells through apoptosis (Abstract). The authors disclose that antioxidants have been associated with a reduced risk of cancer in various tissues, including the prostate (page 288, left column). Three prostate cancer cell lines, DU-145 (androgen-unresponsive), LNCaP (androgen-responsive) and ALVA-101 (androgen moderately responsive) were used to test the effects of several antioxidants, including α-tocopherol on cell growth in culture (*id.* at right column). α-Tocopherol produced significant growth suppression of ALVA-101 and LNCaP cells compared to control (page 289, left column). The authors further disclose that androgens increase oxidative stress in androgen-responsive but not androgen-unresponsive cells such as PC-3 (page 292, left column). Vitamin E did not cause growth inhibition of in the androgen-unresponsive (DU-145) human prostate cancer cell lines, whereas it did significantly affect the growth of the androgen-responsive cell lines (*id.*). In summary, the authors conclude that the results suggest that antioxidants may retard human prostate cancer cell growth through mechanisms that activate apoptosis (page 292, right column).

Sheu *et al.* compare the activities of α-tocopherol and PMC (2,2,5,7,8-pentamethyl-6-hydroxychromane) on platelet aggregation and antioxidant activity (Abstract). PMC is the same compound recited in instant claims 2 and 6 and is disclosed to be a "potent antioxidant derived from α-tocopherol" (Abstract).



α-Tocopherol (Vitamin E)



PMC

PMC is more hydrophilic than other α-tocopherol derivatives and has potent radical scavenging activity (page 198). PMC was shown to have greater antioxidant activity than α-tocopherol (page 204). The authors conclude that the antioxidant activities of PMC in various radical-mediated pathological events, particularly in *in vivo* situations, should be further studied (page 205).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art clearly discloses that α-tocopherol has activity in inhibiting androgen-dependent prostate cancer cell growth possibly due to its antioxidant activity. Further, Sheu *et al.* demonstrate that the antioxidant activity of α-tocopherol is mainly due to the chroman head group (PMC vs. α-tocopherol).

The prior art differs from the instant claims in that it does not explicitly disclose that the instantly claimed compounds have antiandrogenic activity.

It is clear from the instant disclosure that the anti-androgenic activity of chromanol-derived moiety is believed by the inventors to be a newly discovered property (page 5, lines 11-15). However, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Thus, the instantly claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is clear from the prior art that vitamin E was effective in inhibiting the growth of androgen-dependent prostate cancer cells. While the effect was thought to be due to the antioxidant activity of vitamin E, the fact that vitamin E was not effective in inhibiting androgen-independent cell growth would lead the skilled artisan to believe that vitamin E has antiandrogenic activity, whether through its antioxidant properties or through direct binding to androgen receptors.

Sheu *et al.* provide the skilled artisan with the motivation to use chromanol-derived vitamin E compounds to inhibit prostate cancer cells. It is clear from this article that the antioxidant properties of vitamin E are due to the chroman head group as PMC is a more active antioxidant when compared to vitamin E. As such, the skilled artisan would have been imbued with at least a reasonable expectation that PMC would be effective in inhibiting androgen-dependent prostate cancer cell growth, whether through

antioxidant activity or some other mechanism of action. The fact that applicants discovered that the claimed compounds are anti-androgens does not render the instant claims less obvious over the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

January 30, 2007